FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
1565	09/806639

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP 99/07254	SEPTEMBER 30, 1999	OCTOBER 2, 1998

TITLE OF INVENTION

USE OF TESTOSTERONE ESTERS AND/OR TESTOSTERONE FOR PRODUCING BUCALLY APPLICABLE BIO-ADHESIVE SYSTEMS WITH TIME-RELEASED ACTIVE INGREDIENTS

APPLICANT(S) FOR DO/EO/US

Dorie HUEBLER, Guenter KAUFMANN, Michael OETTEL, Holger ZIMMERMANN, Michael DITTGEN, Sabine FRICKE, Manfred BOESE, Ralf LADWIG, Sven CLAUSSEN, Carsten TIMPE

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ Certificate of Mailing by Express Mail
19. ☐ Other items or information:

EF215953247 US

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR) 09/806639	INTERNATIONAL APPLICATION NO. PCT/EP 99/07254	ATTORNEY'S DOCKET NUMBER 1565

20. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐ Search Report has been prepared by the EPO or JPO	$930.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482)	$720.00	
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	$790.00	
☒ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO	$1,070.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$98.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =	$1,000.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	6 - 20 =	0	x $18.00	$0.00	
Independent claims	1 - 3 =	0	x $80.00	$0.00	
Multiple Dependent Claims **(check if applicable).**			☐	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$1,000.00	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).** ☐				$0.00	
SUBTOTAL =				$1,000.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00	
TOTAL NATIONAL FEE =				$1,000.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				$0.00	
TOTAL FEES ENCLOSED =				$1,000.00	
				Amount to be: refunded	$
				charged	$

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **19-4675** in the amount of **$1,000.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **19-4675** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

MICHAEL J. STRIKER
NAME

27233
REGISTRATION NUMBER

APRIL 2, 2001
DATE

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Group: Attorney Docket # 1565

Applicant(s) : HUEBLER, D., ET AL

Serial No. :

Filed : Simultaneously

For : USE OF TESTOSTERONE ESTERS AND/OR TESTOSTERONE FOR PRODUCING BUCALLY APPLICABLE BIO-ADHESIVE SYSTEMS WITH TIME-RELEASED ACTIVE INGREDIENTS

SIMULTANEOUS AMENDMENT

April 2, 2001

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

S I R S:

Simultaneously with filing of the above identified application please amend the same as follows:

In the Claims:

Cancel all claims without prejudice.

Substitute the claims attached hereto.

REMARKS:

This Amendment is submitted simultaneously with filing of the above identified application.

With the present Amendment applicant has amended the claims so as to eliminate their multiple dependency.

Consideration and allowance of the present application is most respectfully requested.

Respectfully submitted,

Michael J. Striker
Attorney for Applicant(s)
Reg. No. 27233

Patentansprüche

1. Verwendung von Testosteronestern mit 1 bis 20 C-Atomen im Carbonsäurerest oder Mischungen aus zwei oder mehreren Testosteronestern mit unterschiedlichen Carbonsäureresten und/oder Testosteron zur Herstellung von bukkal applizierbaren bioadhäsiven Systemen mit zeitlich gesteuerter Wirkstofffreisetzung zur Behandlung von Erkrankungen, welche mit einem veränderten Testosteronspiegel einhergehen.

2. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die Kohlenstoffgerüste der Carbonsäurereste gradkettig, verzweigt, alicyclisch, gesättigt und/oder ungesättigt mit bis zu fünf Doppel- und/oder Dreifachbindungen sind.

3. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß das Verhältnis von Testosteron zu Testosteronester 1 : 100 bis 1 : 1, vorzugsweise 1 : 10 bis 1 : 1,5 beträgt.

4. Verwendung gemäß Anspruch 1, dadurch gekennzeichnet, daß die bukkal zu applizierenden bioadhäsiven Systeme erhältlich sind, indem man die Wirkstoffe zunächst getrennt oder gemeinsam in einem Sprühtrocknungsverfahren amorph in organische Polymere eingebettet.

5. Verwendung gemäß Anspruch 4, dadurch gekennzeichnet, daß man die amorphen Testosteron-Sprühprodukte zusammen mit anderen Hilfsstoffen, Bindemitteln, Füllmitteln, Gleitmitteln, bioadhäsiven Polymeren, Tensiden, Zerfallsbeschleunigern mischt und zu Ein- oder Mehrschichttabletten verpreßt.

6. Verwendung gemäß Anspruch 1 zur gezielten Einstellung therapeutischer und/oder zirkadianer Rhythmen der Testosteronspiegel.

USE OF TESTOSTERONE ESTERS AND/OR TESTOSTERONE FOR PRODUCING BUCCALLY APPLICABLE BIO-ADHESIVE SYSTEMS WITH TIME-RELEASED ACTIVE INGREDIENTS

The invention relates to a combination of testosterone and testosterone esters (or to the sole use of testosterone esters) in a buccal, bioadhesive preparation so that, by finely adjusted dosing of the active ingredients and ester selection, various desired plasma levels of testosterone can be set or produced in individual patients, for example to restore an endogenous circadian body rhythm.

Testosterone is quantitatively and qualitatively the most important androgen synthesized in the body. It is formed mainly in the testicles and in small amounts in the adrenal glands and in women in the ovaries. In males, testosterone is responsible for the development of the male characteristics during fetal, neonatal and pubertal maturation and finally for attaining the male phenotype and for androgen-dependent functions (for example spermatogenesis). Testosterone exerts protein-anabolic action (in muscles, bones, hematopoiesis, kidneys and liver) {E. Mutschler, "Arzneimittelwirkungen" [Drug Actions], 6th edition, pp. 334-337, Wissenschaftliche Verlagsgesellschaft mbh [publisher], Stuttgart, 1991}.

After oral or parenteral administration, testosterone is rapidly absorbed in the gastrointestinal tract. It is then transported by the portal vein to the liver where it is rapidly metabolized. As a result, the plasma half-life of testosterone is short, i.e., about 10 minutes {Auterhoff, H., Knabe, J. and Höltje, H.D., "Lehrbuch der Pharmazeutischen Chemie" [Textbook of Pharmaceutical Chemistry], 12th edition, pp. 570-573, Wissenschaftliche Verlagsgesellschaft mbh [publisher], Stuttgart, 1991}. To develop a physiological serum level, oral administration of 400 mg (!) of testosterone is needed (S.G. Johnson, E.P. Bennet and V.G. Jensen, Therapeutic effectiveness of oral testosterone, Lancet 2:1974, 1473-1475).

To prolong the action of testosterone, testosterone esters with varying chain length (testosterone propionate, testosterone enantate, testosterone undecanoate) are injected intramuscularly as an oily solution or suspension. It is known that in contact with body fluids these esters will slowly hydrolyze under the action of esterases thus releasing the pharmacologically active testosterone. The influence of the type of ester on the growth of the capon comb after i.m. injection has already been described (Meier, R. and Tschopp, E., Arch. Exptl. Pathol. Pharmacol. 226:1955, 532).

Moreover, testosterone undecanoate (in oleic acid, as a soft gelatin capsule) is administered orally via the lymphatic route [Andriol® preparation]. From the oleic acid-embedded preparation, the drug passes from the gastrointestinal tract through the thoracic duct into the lymph tract thus reaching the systemic circulation. This gives rise to varying serum levels and gastrointestinal side effects. These effects can make long-term replacement therapy difficult (A.M. Matsumoto: Hormonal therapy of male hypogonadism, Endocrinol. Metab. Clin. North Am. 23:1994, 857-875).

Other routes of administration (transdermal, nasal, sublingual, buccal, subcutaneous) have been studied by various research groups (for example, by N.A. Mazer, W.E. Heiber, J.F. Moellmer, A.W. Meikle, J.D. Stringham, S.W. Sanders, K.G. Tolman and W.D. Odell, Enhanced transdermal delivery of testosterone: A new physiological approach for androgen replacement in hypogonadal men, J. Controll. Rel. 19:1992, 347-362).

Drawbacks of the aforesaid therapies are: 1. either a too short, rapidly decreasing testosterone level (after oral administration) or 2. - in the case of intramuscular injection of testosterone esters - the fact that a constantly set testosterone level cannot be changed over a long period of time (days to weeks) thus not allowing individual time control of the testosterone action. Moreover, down regulation of the basal testosterone secretion can take place.

The low bioavailability caused by the high first-pass effect in the liver can be circumvented by buccal or sublingual administration. Various studies confirm this (for example, Pitha, J., Anaissie, J. and Uekama, K., g-Cyclodextrin: Testosterone complex suitable for sublingual administration, J. Pharmaceutical Sciences 76 (10):1987, 788-790).

Buccal administration of drugs is known from the prior art.

EP-0371466 A concerns a rapidly soluble tablet for fast buccal administration of steroids, among other things (for example estrogens, progestins). The main ingredient used is a water-soluble polyhydric alcohol, particularly sorbitol. The advantage is a rapid initial increase in drug concentration.

EP-0286581 A discloses the transmucosal buccal administration of estrogens (17β-estradiol and ethinylestradiol). The estrogen is used within the framework of hormone replacement therapy in postmenopausal women for treating PMS (postmenopausal syndrome) and for osteoporosis therapy at a dose of 50-100 μg/day (17β-estradiol for PMS therapy) and at a dose of 200-400 μg/day (17β-estradiol for osteoporosis therapy). Buccal administration makes it possible to attain therapeutic plasma levels by circumventing the first-pass effect.

WO-704342 describes a special formulation said to be particularly suitable for, among other things, the buccal administration of estrogens (for example estradiol and the esters of estradiol), progestins, androgens and anabolic steroids. This formulation contains a) about 1 - 20% of a soluble, adhesive polymer (carbomers, partly hydrolyzed polyvinyl alcohol [PVA], polyethylene oxide, polyacrylate, hydroxypropylmethylcellulose), b) a soluble, directly tabletted auxiliary agent and c) the active ingredient. The adhesive polymer makes the formulation or drug form adhere at the site of administration.

US-4396615-A describes the treatment of androgen-related diseases by administration of 6-methylene-progesterone, a testosterone-5α-reductase inhibitor, in the form of topical formulations. Such formulations contain the inhibitor and an inert topical carrier (for example, a silicone, methylcellulose,

hydroxymethylcellulose).

CA-2105887-A discloses a bioerodable system for buccal and vaginal administration of hormones (estradiol), among other things. The system is water-soluble and mucoadherent. It consists of a solid, soluble, lyophilized foam and the active ingredient . The disintegration time is at least 8 hours. The system adheres to the mucosal membrane where it releases the drug. The polymers used are primarily gelatin, sodium carboxymethylcellulose, methylcellulose etc. A particular advantage of the system is its long adhesion time.

As regards the tailored time-release control of drugs, note that it is not possible for our currently available drugs to provide variable release of the active ingredient nor to adapt the release to the drug needs of an individual patient.

For release-control purposes, current depot drugs use passive dissolution, diffusion, swelling and erosion processes {Gröning, R., "Arzneiformen mit elektronisch gesteuerter Freisetzung" [Drug Forms with Electronically Controlled Release], in "Pharmazeutische Technologie: Moderne Arzneiformen" [Pharmaceutical Technology: Modern Drug Forms], p. 441, ed. [sic - Translator], Müller, R.H. and Hildebrand, G.E. (editors), Wissenschaftliche Verlagsgesellschaft mbh [publisher], Stuttgart, 1998}.

The time-controlled release of drugs is also known from the prior art.

JP-07118143 discloses time-controlled capsules which a) are water-insoluble or partly water-soluble, b) consist of water-swellable substances (powder, granulates or pills of, for example, calcium carboxymethylcellulose or polyvinylpyrrolidone) and c) contain elements (tablets) with the active ingredient in the center of the capsule.

The prior art also describes sustained-release preparations using polymers. Thus EP-068446, for example, discloses the use of methylcellulose or carboxymethylcellulose in sustained-release mixtures.

The object of the present invention is to make use of the advantages of buccal administration of steroids with high first-pass effect and low bioavailability, especially of testosterone and the esters thereof, by exploiting the different pharmacokinetics of the various testosterone esters (depending on chain length), so as to be able, by careful selection of appropriate dosages and esters, to attain a desired drug profile.

This objective is reached by use of testosterone esters with 1 to 20 carbon atoms in the carboxylic acid radical or of a mixture of two or more testosterone esters with different carboxylic acid radicals and/or testosterone, for the preparation of buccally administered bioadhesive systems with time-controlled release of the active ingredient, for treating diseases associated with a modified testosterone level.

Preferably used are testosterone esters wherein the carbon structure of the carboxylic acid radical is linear, branched, alicyclic, saturated and/or unsaturated and contains up to five double and/or triple bonds.

Also preferred is a ratio of testosterone to testosterone ester from 1 : 100 to 1 : 1 and particularly from 1 : 10 to 1 : 1.5.

It is particularly preferred that the buccally administered bioadhesive systems be prepared by first embedding into an organic polymer the active ingredients, separately or together, in an amorphous state as obtained by use of a spray-drying process.

It is especially preferred to mix the amorphous, spray-dried testosterone products with other auxiliary agents, binders, fillers, lubricants, bioadhesive polymers, surfactants or disintegration accelerators and to compress the mixture into single-layer or multilayer tablets.

The use for a tailored adjustment of therapeutic and/or circadian rhythms of the testosterone levels is preferred.

Surprisingly, we have now found that the chain length of the testosterone ester not only determines the solubility, but, as was shown experimentally, evidently also the kinetics of ester cleavage in the blood or tissue fluids by the corresponding hydrolases. Note in particular, when testosterone esters are employed, the use of the embedding technique of spray-drying in organic polymers (polyvinylpyrrolidone, hydroxypropylmethylcellulose, solid polyethylene glycols) to achieve improved solubility in the oral cavity. This is particularly important in view of the small saliva volumes (about 1 - 1.5 mL) which here, on the average, are available for the dissolution of sparingly soluble esters. In the publication by Jody Voorspoels [Vorspoels, J., Remon, J.P., Eechaute, W.E. and De Sy, W., Buccal Absorption of Testosterone and Its Esters Using a Bioadhesive Tablet in Dogs, Pharmaceutical Research, vol. 13, No. 8, 1996, 1228-1232), the testosterone esters (testosterone acetate, testosterone propionate, testosterone enantate, testosterone decanoate) studied in six castrated beagle dogs did not show a higher bioavailability than testosterone in spite of their higher lipophilicity. Because the esters were directly compressed only after dry mixing, without using a special premixing technology (amorphization by spray-drying), these poorer results presumably are due to the low, and in some cases extremely low, solubility of the esters in the crystalline state.

We were able to show that by the use of buccal administration of testosterone in combination with testosterone esters of different chain length, it is possible to attain different blood level patterns or rhythms (such as a circadian rhythm). In selecting the testosterone ester, the choice can be made specifically from three groups: 1. esters of shorter chain length (for example, testosterone acetate or propionate), 2. esters of medium chain length (for example testosterone enantate, cipionate or cyclohexanecarboxylate) and 3. esters of higher chain length (for example testosterone undecanoate, or

bucyclate).

According to the invention, this objective is reached by dissolving testosterone or the particular testosterone ester together with the polymer (for example polyvinylpyrrolidone or hydroxypropylmethylcellulose) in ethanol and processing the mixtures further in a spray-drying unit to form an amorphous, embedded, spray-dried formulation. It is possible in this case 1) to embed said active ingredients separately from each other or 2) to embed them together in a single processing step, to obtain an amorphous mixture.

The fine-particle embedded spray-dried material is then subjected to dry mixing with other auxiliary agents for making bioadhesive buccal tablets [binders: polyvinylpyrrolidone, cellulose ethers; fillers: Cellactose®, mannitol, sorbitol, lactose; lubricants: magnesium stearate, hydrogenated vegetable fats; bioadhesive polymers: polyacrylates (Carbopols®, sodium carboxymethylcellulose) and optionally other auxiliary agents, such as surfactants or disintegration accelerators]. The mixture is then compressed into buccal tablets which can have a layered structure (active ingredient layer, bioadhesive layer; unidirectional or multidirectional release).

Based on blood level studies with the individual drug components alone, it is possible to attain the appropriate release patterns by changing the following two parameters

- dosage of the active ingredient
- selection of the ester or of the chain length at C-17.

An advantageous combination is, for example, that of the short-acting testosterone with testosterone undecanoate (eleven-carbon chain) which has a longer half-life (see practical examples).

To this end, an advantageous ratio of the active ingredients, namely of testosterone to Σ testosterone esters, is from 1 : 100 to 1 : 1 and particularly from 1 : 10 to 1 : 1.5.

By skillful combination of testosterone with testosterone esters, it is possible to attain blood level patterns which are capable of recreating or simulating the body's own rhythmicity of endogenous testosterone levels. For example, the duration of action of a bioadhesive buccal tablet with testosterone can be prolonged by combining testosterone with testosterone undecanoate (cf. Fig. 1 and Fig. 3). In the practical example (equimolar combination), the duration of blood levels of > 100 ng/mL is increased in female dogs from 2 to 4 hours. Moreover, a marked (slower) pulse is reached with a maximum appearing after about 3 hours. After 8 h, the testosterone values of nearly 50 ng/mL are still double as high as those attained with testosterone alone.

In essence, the set blood level pattern of testosterone is controlled through two parameters:

* The chain length and steric structure of the ester chain at C-17. This structure determines, on the one hand, the lipophilicity and thus the solubility and, on the other, in a pronounced manner, the rate of ester cleavage and hydrolysis (interactions of the ester side chain with the active center of hydrolases). For example, esters with a longer chain length are cleaved more slowly than those with an intermediate or shorter chain length. In this sense, the released testosterone becomes available more slowly than after administration of pure testosterone, i.e. the peak appears later. Through the chain length, it is thus possible to attain a more or less tailored time control of therapeutic action.

* The dosage of testosterone or of the testosterone esters on the basis of direct proportionality between the area under the curve [AUC] and the dose given.

This could be important for hormone replacement therapy in elderly men with partial androgen deficiency (PADAM patients) in that a deficient plasma level could be appropriately corrected.

The following practical examples illustrate the invention without limiting its scope.

EXAMPLE 1

Bioadhesive Tablet with Testosterone

Formulation

Component	Weight/tablet
Active ingredient layer	
Testosterone premix (20%)	50.00
Mannitol	43.90
Cellactose 80	29.50
Carmellose sodium	1.20
Magnesium stearate	1.50
Talc	4.50
Adhesive layer	
Mannitol	17.40
Cellactose 80	34.82
Carmellose sodium	10.18
Magnesium stearate	0.65
Red iron oxide	0.05
Talc	1.90

Preparation:

Preparation of the Premix

The testosterone premix (20%) was prepared by spray-drying. To this end, the active ingredient together with the polymer (for example, polyvinylpyrrolidone, hydroxypropylmethylcellulose) and optionally another auxiliary agent (carrier or antistatic agent) were dissolved or suspended in an appropriate solvent. The homogenized suspension obtained by steady stirring was spray-dried in a spray-drying unit to obtain a fine powder.

Preparation of the Active Ingredient Layer

This premix was mixed with the other auxiliary agents for the active ingredient layer (mannitol, Cellactose 80) in an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc) for about 20 minutes. The outer phase (Carmellose sodium, magnesium stearate, talc) was then added, and mixing was continued for 5 minutes.

Preparation of the Adhesive Layer

Red iron oxide and talc were intimately ground in a ball mill. In an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc), mannitol and Cellalactose 80 were mixed for about 20 min. The ground colored mixture, Carmellose sodium and magnesium stearate were then added as the outer phase, and mixing was continued for an additional 5 minutes.

The mixtures for the active ingredient layer and adhesive layer, in the weight ratio given, were then compressed in an appropriate tabletting press to form two-layer tablets.

Fig. 1 shows the blood level variation for a formulation according to Example 1.

EXAMPLE 2

Bioadhesive Tablet with Testosterone Undecanoate

Formulation

Component	Weight/tablet
Active ingredient layer	
Testosterone undecanoate premix (20%)	50.00
Mannitol	43.90
Cellactose 80	29.50
Carmellose sodium	1.20
Magnesium stearate	1.50
Talc	4.30
Adhesive layer	
Mannitol	17.40
Cellactose 80	34.82
Carmellose sodium	10.18
Magnesium stearate	0.65
Red iron oxide	0.05
Talc	1.90

Preparation:

Preparation of the Premix

The testosterone undecanoate premix (20%) was prepared by spray-drying. To this end, the active ingredient together with the polymer (for example, polyvinylpyrrolidone, hydroxypropylmethylcellulose) and optionally another auxiliary agent (carrier or antistatic agent) were dissolved or suspended in an appropriate solvent. The homogenized suspension obtained by steady stirring was spray-dried in a spray-drying unit to obtain a fine powder.

Preparation of the Active Ingredient Layer

This premix was mixed with other auxiliary agents for the active ingredient layer (mannitol, Cellactose 80) in an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc) for about 20 minutes. The outer phase (Carmellose sodium, magnesium stearate, talc) was then added, and mixing was

continued for 5 minutes.

Preparation of the Adhesive Layer

Red iron oxide and talc were intimately ground in a ball mill. In an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc), mannitol and Cellalactose 80 were mixed for about 20 min. The ground colored mixture, Carmellose sodium and magnesium stearate were then added as the outer phase, and mixing was continued for an additional 5 minutes.

The mixtures for the active ingredient layer and adhesive layer, in the weight ratio given, were then compressed in an appropriate tabletting press to obtain two-layer tablets.

Fig. 2 shows the blood level variation for a formulation according to Example 2

EXAMPLE 3

Bioadhesive Tablet with Testosterone and Testosterone Undecanoate

Formulation

Component	Weight/tablet
Active ingredient layer	
Testosterone/ testosterone undecanoate premix (20%, 20%)	50.00
Mannitol	43.90
Cellactose 80	29.50
Carmellose sodium	1.20
Magnesium stearate	1.50
Talc	4.30
Adhesive layer	
Mannitol	17.40
Cellactose 80	34.82
Carmellose sodium	10.18
Magnesium stearate	0.65
Red iron oxide	0.05
Talc	1.90

Preparation of the Premix

The testosterone/testosterone undecanoate premix (20%) was prepared by spray-drying. To this end, the active ingredient together with the polymer (for example, polyvinylpyrrolidone, hydroxypropylmethylcellulose) and optionally another auxiliary agent (carrier or antistatic agent) were dissolved or suspended in an appropriate solvent. The homogenized suspension obtained by steady stirring was spray-dried in a spray-drying unit to obtain a fine powder.

Preparation of the Active Ingredient Layer

This premix was mixed with other auxiliary agents for the active ingredient layer (mannitol, Cellactose 80) in an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc) for about 20 minutes. The outer phase (Carmel-lose sodium, magnesium stearate, talc) was then added, and mixing was continued for 5 minutes.

Preparation of the Adhesive Layer

Red iron oxide and talc were intimately ground in a ball mill. In an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc), mannitol and Cellalactose 80 were mixed for about 20 min. The ground colored mixture, Carmellose sodium and magnesium stearate were then added as the outer phase, and mixing was continued for an additional 5 minutes.

The mixtures for the active ingredient layer and adhesive layer, in the weight ratio given, were then compressed in an appropriate tabletting press to form two-layer tablets.

Fig. 3 shows the blood level variation for a formulation according to Example 3.

EXAMPLE 4

Bioadhesive Tablet with Testosterone and Testosterone Enantate

Formulation

Component	Weight/tablet
Active ingredient layer	
Testosterone/ testosterone enantate premix (20%, 20%)	50.00
Mannitol	58.60
Emcompress	14,00
Carbopol® 974	2.00
Magnesium stearate	1.50
Talc	4.30
Adhesive layer	
Mannitol	17.40
Emcompress	34.82
Carbopol® 974	13.00
Magnesium stearate	0.65
Red iron oxide	0.05
Talc	1.90

Preparation:

Preparation of the Premix

The testosterone/testosterone enantate premix (20%) was prepared by spray-drying. To this end, the active ingredient together with the polymer (for example, polyvinylpyrrolidone, hydroxypropylmethyl-cellulose and optionally another auxiliary agent (carrier or antistatic agent) were dissolved or suspended in an appropriate solvent. The homogenized suspension obtained by steady stirring was spray-dried in a spray-drying unit to form a fine powder.

Preparation of the Active Ingredient Layer

This premix was mixed with other auxiliary agents for the active ingredient layer (mannitol, Emcompress) in an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc) for about 20 minutes. The outer phase (Carbopol® 974, magnesium stearate, talc) was then added, and mixing

was continued for 5 minutes.

Preparation of the Adhesive Layer

Red iron oxide and talc were intimately ground in a ball mill. In an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc), mannitol and Emcompress were mixed for about 20 min. The ground colored mixture, Carbopol® 974 and magnesium stearate were then added as the outer phase, and mixing was continued for an additional 5 minutes.

The mixtures for the active ingredient layer and adhesive layer, in the weight ratio given, were then compressed in an appropriate tabletting press to form two-layer tablets.

EXAMPLE 5

Bioadhesive Tablet with Testosterone Propionate and Testosterone Undecanoate

Formulation

Component	Weight/tablet
Active ingredient layer	
Testosterone propionate/ testosterone enantate premix (20%, 20%)	50.00
Mannitol	58.60
Emcompress	14.00
Carbopol® 974	2.00
Magnesium stearate	1.50
Talc	4.30
Adhesive layer	
Mannitol	17.40
Emcompress	34.82
Carbopol® 974	13.00
Magnesium stearate	0.65
Red iron oxide	0.05
Talc	1.90

Preparation:

Preparation of the Premix

The testosterone propionate/testosterone undecanoate premix (20%) was prepared by spray-drying. To this end, the active ingredient together with the polymer (for example, polyvinylpyrrolidone, hydroxypropylmethylcellulose) and optionally another auxiliary agent (carrier or antistatic agent) were dissolved or suspended in an appropriate solvent. The homogenized suspension obtained by steady stirring was spray-dried in a spray-drying unit to obtain a fine powder.

Preparation of the Active Ingredient Layer

This premix was mixed with other auxiliary agents for the active ingredient layer (mannitol, Emcompress) in an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc) for about 20 minutes. The outer phase (Carbopol® 974, magnesium stearate, talc) was then added, and mixing was continued for 5 minutes.

Preparation of the Adhesive Layer

Red iron oxide and talc were intimately ground in a ball mill. In an appropriate mixer (type: Kubu mixer, Turbula mixer, tumble mixer etc), mannitol and Emcompress were mixed for about 20 min. The ground colored mixture, Carbopol® 974 and magnesium stearate were then added as the outer phase, and mixing was continued for an additional 5 minutes.

The mixtures for the active ingredient layer and adhesive layer, in the weight ratio given, were then compressed in an appropriate tabletting press to form two-layer tablets.

PATENT CLAIMS

1. Use of testosterone esters with 1 to 20 carbon atoms in the carboxylic acid radical or of mixtures of two or more testosterone esters with different carboxylic acid radicals and/or of testosterone for preparing buccally administered bioadhesive systems with time-controlled active ingredient release, for treating diseases associated with a modified testosterone level.

2. Use according to Claim 1, characterized in that the carbon structures of the carboxylic acid radicals are linear, branched, alicyclic, saturated and/or unsaturated and have up to five double and/or triple bonds.

3. Use according to Claim 1 or 2, characterized in that the ratio of testosterone to testosterone ester is from 1 : 100 to 1 : 1 and preferably from 1 : 10 to 1 : 1.5.

4. Use according to one of Claims 1 to 3, characterized in that the buccally administered bioadhesive systems are obtained by first embedding the amorphous active ingredients as obtained by a spray-drying process, separately or conjointly, into an organic polymer.

5. Use according to Claim 4, characterized in that the amorphous spray-dried testosterone products are mixed with other auxiliary agents, binders, fillers, lubricants, bioadhesive polymers, surfactants or disintegration accelerators, and the mixture is then compressed to form single-layer or multilayer tablets.

6. Use according to one of the preceding claims for the purpose of attaining in a tailored manner a therapeutic and/or circadian rhythm of the testosterone level.

ABSTRACT

The use of testosterone esters with 1 to 20 carbon atoms in the carboxylic acid radical or of mixtures of two or more testosterone esters with different carboxylic acid radicals and/or of testosterone, for producing buccally administered bioadhesive systems with time-controlled release of the active ingredient for the treatment of diseases associated with a modified testosterone level.

The use according to the invention makes it possible to attain in a tailored manner a therapeutic and/or circadian rhythm of the testosterone level.

Fig. 1

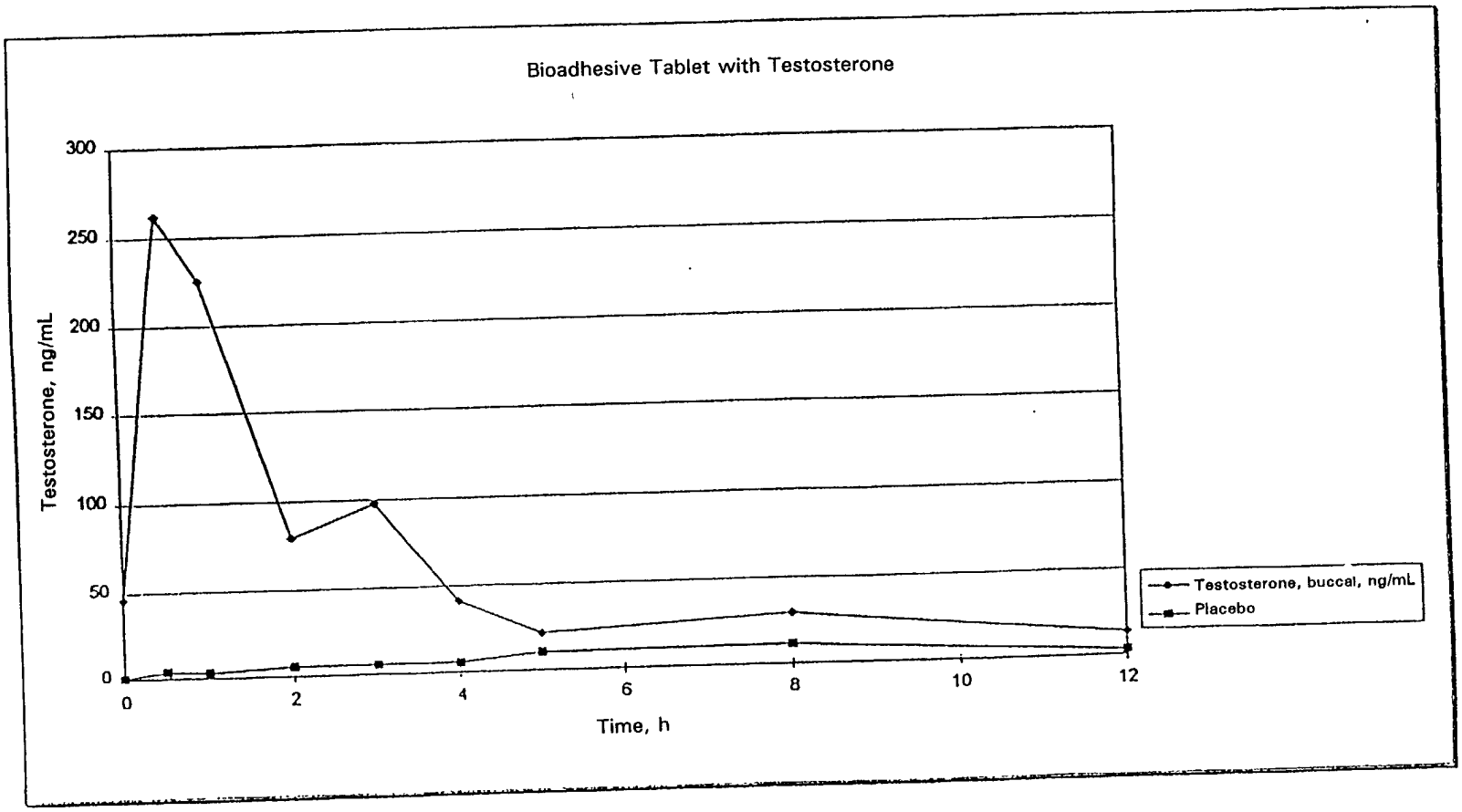


Fig. 2

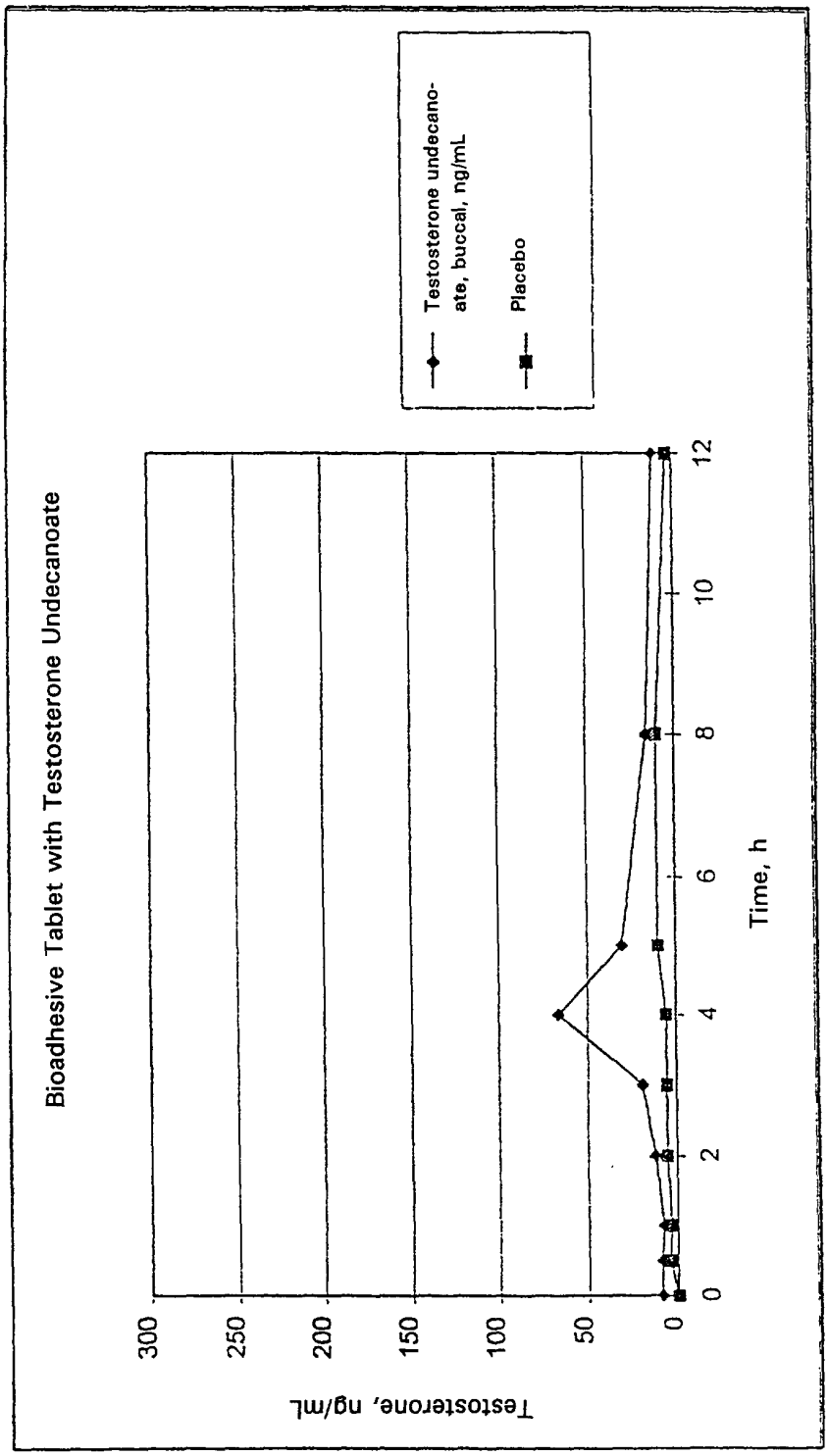
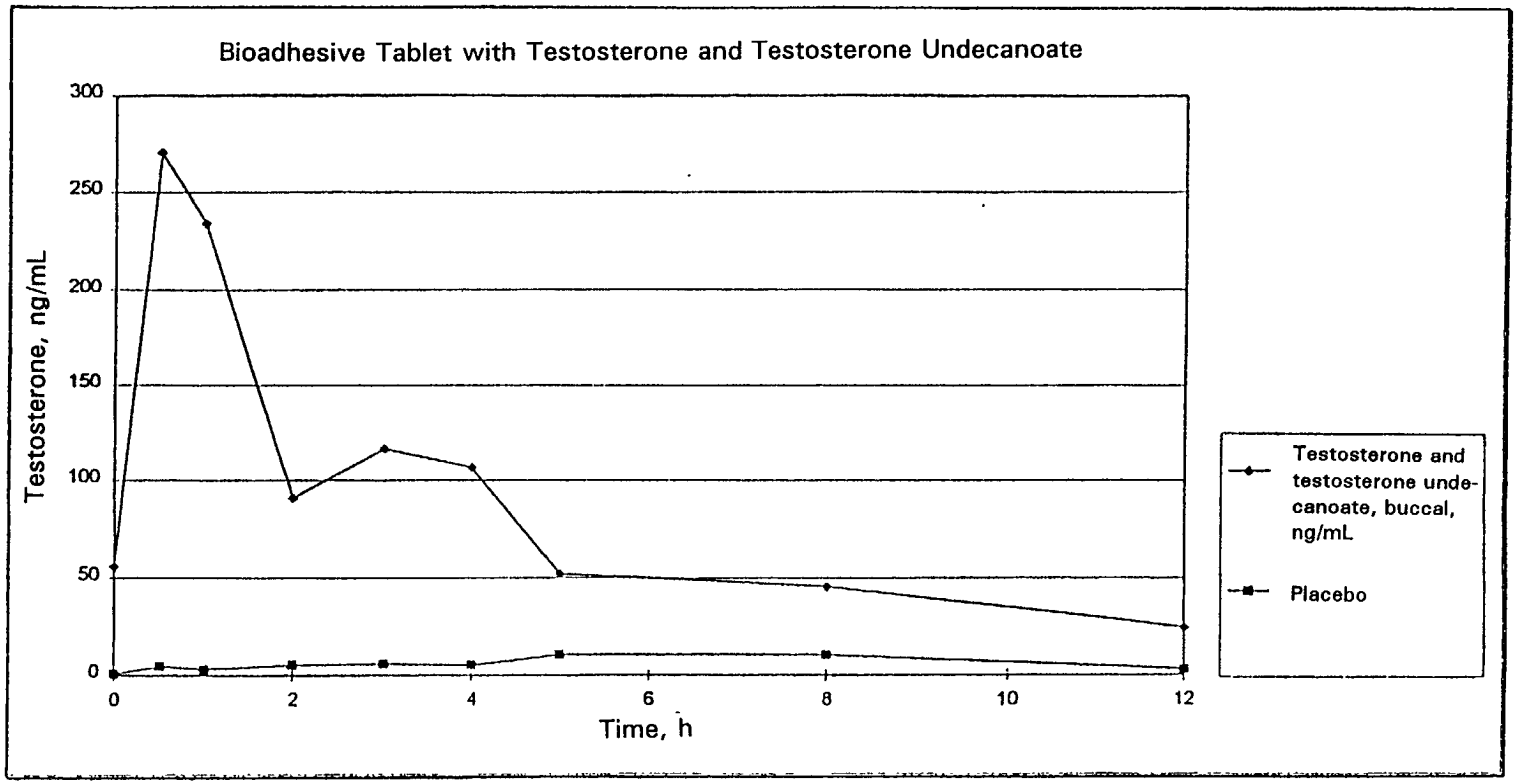


Fig. 3


Bioadhesive Tablet with Testosterone and Testosterone Undecanoate
Testosterone, ng/mL
300
250
200
150
100
50
0
0
2
4
6
8
10
12
Time, h
Testosterone and testosterone undecanoate, buccal, ng/mL
Placebo

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Group: Attorney Docket # 1565

Applicant(s): HUEBLER, D., ET AL

Serial No.: 09/806,639

Filed: 04/02/2001

For : USE OF TESTOSTERONE ESTERS AND/OR TESTOSTERONE FOR PRODUCING BUCALLY APPLICABLE BIO-ADHESIVE SYSTEMS WITH TIME-RELEASED ACTIVE INGREDIENT

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

May 16, 2001

Sir:

The subject application was filed without the signature of the inventors and in the German language.

Declaration papers executed by the inventors and a Certified English Translation of the application are submitted herewith.

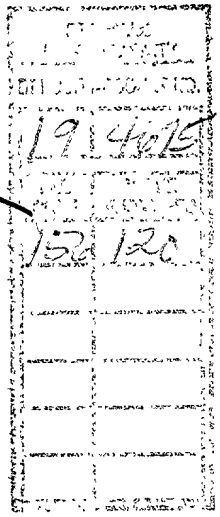
It is respectfully requested that the required fee be charged to the account of the undersigned (19-4675).

Box: PCT

Respectfully submitted,

Michael J. Striker
Attorney for Applicant(s)
Reg. No. 27233

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.
On 5/17/01



I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

60/106,520	NOVEMBER 3, 1998
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Docket No.
1565

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

USE OF TESTOSTERONE ESTERS AND/OR TESTOSTERONE FOR PRODUCING BUCALLY APPLICABLE BIO-ADHESIVE SYSTEMS WITH TIME-RELEASED ACTIVE INGREDIENTS

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on **SEPTEMBER 30, 1999** as United States Application No. or PCT International Application Number **PCT/EP 99/07254**

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
198 47 252.8	GERMANY	October 2, 1998	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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